Position statement regarding newborn screening for muscular dystrophy

Background

Muscular dystrophies are a group of inherited disorders characterised by progressive weakness and wasting of the muscles that control body movement. Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy in childhood and is therefore the focus of this statement. It is caused by mutations in the DMD gene, which lies on the X chromosome. This explains why the vast majority of those affected are boys.

The DMD gene encodes the muscle protein dystrophin. Dystrophin links extracellular connective tissue to the internal scaffolding (cytoskeleton) of the muscle cells. This acts as a 'shock absorber', protecting the muscles from repeated contraction and relaxation. If dystrophin is missing, this link is broken, and the muscle is weakened and progressively damaged by normal activity. Eventually the muscle fibres die and are replaced by connective and fatty tissue, and the muscle stops functioning. This process can affect all muscles in the body, including the heart and respiratory muscles.[1] This makes DMD a fatal condition, shortening life, usually through respiratory complications. There have been improvements in life expectancy for the condition over time that have been attributed to improvements in treatment, particularly the provision of respiratory support in the advanced stages of the disease.[2,3] Some affected individuals are now living into their 30s.[4]

Treatment

In considering the possibility of DMD screening, a central issue is the absence of a cure or effective intervention.

The only treatment reported to slow the decline of muscle strength and function in DMD is glucocorticoid treatment.[5] This treatment also reduces the risk of scoliosis, stabilises lung function and may improve heart function. The aim of corticosteroid treatment is to maintain the ability to walk and minimise the risk of other later complications.

It has been reported that spinal surgery is preferred over orthoses for scoliosis. Spinal orthoses has not been demonstrated in studies to prevent or significantly delay scoliosis.[6] It is unclear if spinal fusion for scoliosis improves or stabilises respiratory function. A recent Cochrane review[7] highlighted that different studies have reached different conclusions on the effect of treatment on respiratory function. The most recent publication was an observational study published in 2013 that concluded that the severity of scoliosis was not a key determinant of respiratory dysfunction. In their group, posterior spinal fusion did not reduce the rate of respiratory function decline.[8]

There have been limited studies into beta agonists, which can improve the strength and function of healthy and diseased muscle. The latest study,[9] from 2008, focused on 14 boys (12 DMD and two Beckers). The researchers found that, within the treatment group, there was an increase in lean body mass, a decrease in fat mass and improved functional measures. There was less muscle strength improvement than in the pilot study. Investigators attributed this to the different pharmacokinetics.

Development of genetic treatments (gene therapy) has been slowed due to the large size of the DMD gene and the fact that it is widely expressed in all muscle types and in the central nervous system.[10]

Trials have been conducted in Europe on exon skipping compounds used to treat DMD. However, the results are not showing a significant difference between those boys who were treated and those on a placebo.

---

1 www.ncbi.nlm.nih.gov/pubmed?term=23465426

2 www.ncbi.nlm.nih.gov/pubmed/20581335

3 www.ncbi.nlm.nih.gov/pubmed/15106215

4 www.ncbi.nlm.nih.gov/pubmed/19945913

5 www.ncbi.nlm.nih.gov/pubmed/19945913

6 Harvey A, Baker L, Williams K. 2013. Non-surgical prevention and management of scoliosis for children with Duchenne muscular dystrophy: What is the evidence? *Journal of Paediatrics and Child Health*.

7 Cheuk DKL, Wong V, Wraige E, Baxter P, Cole A. Surgery for scoliosis in Duchenne muscular dystrophy. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD005375. DOI: 10.1002/14651858.CD005375.pub3.

8 Alexander WM, Smith M, Freeman BJC, et al. 2013. The effect of posterior spinal fusion on respiratory function in Duchenne muscular dystrophy. *Eur Spine J* 22:411–416.

9 Skura CL Fowler EG, Wetzel GT, et al. 2008. Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy. *Neurology* 70:137–43

10 www.ncbi.nlm.nih.gov/pubmed/21804598

Newborn screening

Newborn screening can be performed using creatine kinase (CK) and if required a second-tier genetic analysis.

In addition to the presence of a suitable test, the National Health Committee has a list of criteria against which decisions about new screening programmes are assessed.[11] These criteria include effective and accessible treatment; reduced mortality or morbidity; health system capacity to support a screening programme; social, ethical and cost-benefit issues.

A number of articles have identified parental acceptance of screening for disorders that affect newborns/children but that have no cure or effective treatment.[12, 13]

There are also advantages to early detection relating to a reduction in diagnostic odyssey and enhanced reproductive autonomy for the family.

Prenatal genetic diagnosis (PGD) is also an option when the condition is detected early in families, along with cascade testing.

DMD screening internationally

The United Kingdom (UK) National Screening Committee does not recommend newborn screening for DMD. It completed reviews of newborn screening for DMD in 2004 and again in 2011.[14] The reviews provide details on the UK's 21 criteria for screening programmes. The 2011 review found that DMD:

- met three of the criteria
- partially met six criteria
- did not meet six criteria
- was unclear or not applicable on six criteria.

Of note, the condition is considered an important health problem (criteria 1), the epidemiology and natural history of the condition is partially understood (criteria 2), the screening test is valid (criteria 5) but does have a relatively low sensitivity (meaning a relatively high proportion of DMD cases are missed).

The review noted that the lack of an available treatment significantly reduces the potential benefit of screening.

DMD is also not currently on the North American recommended uniform screening panel.[15]

Wales screened newborns for DMD for many years. However, screening has been discontinued because the Centers for Disease Control (USA) is no longer providing quality assurance samples and there are issues with obtaining reagents for testing.[16] Data from the 20 years of newborn screening for DMD in Wales has suggested an incidence of 1 in 5266 male births.[17] The incidence in other jurisdictions, including New Zealand, is unknown.

Recommendation for New Zealand

Although some studies suggest screening for DMD may be accepted by parents, newborn screening for DMD is not recommended in New Zealand at this time. The issues include:

- screening assays and quality assurance specimens are not readily available
- there are limited treatment options.

The Ministry of Health will monitor for significant advancements in DMD testing and treatment that could alter this position on a DMD screening programme.

---

11 http://nhc.health.govt.nz/publications/nhc-publications-pre-2011/screening-improve-health-new-zealand

12 Plass AM et al. 2010. Neonatal screening for treatable and untreatable disorders: prospective parents' opinions. *Pediatrics* 125(1): e99-106;

13 Wong SH et al. 2011. 'There's no easy answer': Age at diagnosis of boys with Duchenne muscular dystrophy and parent's views on population screening. *Twin Research and Human Genetics* 14(4): 384.

14 www.screening.nhs.uk/policydb_download.php?doc=196

15 http://onlinelibrary.wiley.com/doi/10.1002/mus.23810/full

16 www.wales.nhs.uk/sitesplus/863/opendoc/182079

17 www.nature.com/ejhg/journal/v21/n10/full/ejhg2012301a.html

MINISTRY OF HEALTH
MANATŪ HAUORA
National Screening Unit
New Zealand Government
www.nsu.govt.nz

November 2014 HP 6068